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Cost-Effectiveness Analysis Of Ceftriaxone-Gentamicin And Ampicillin-Gentamicin In Pediatric Pneumonia At Hospital X Madiun

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ABSTRACT

Pneumonia is an infectious disease caused by bacteria characterized by fever, chills, coughing up phlegm, and breathing difficulty. Generally pneumonia is caused by an infection of Streptococcus pneumoniae bacteria. Antibiotics is a therapy used in pediatric pneumonia patients at hospitals X. in Madiun. This study aims to determine a more cost-effective antibiotics therapy combination between ceftriaxone-Gentamicin and Ampicillin-Gentamicin in pediatric pneumonia patients at Hospital X in Madiun in 2019-2021. This study used a *cross sectional* design and data collection was carried out retrospectively. There were 39 patients as samples who were pediatric patients aged ≤ 12 years who were adjusted to the inclusion criteria. The datawere identified using decision trees and analyzed cost-effectiveness with ACER and ICER calculations. The ACER value of Ceftriaxone-Gentamicin antibiotic therapy is IDR 6,047,334.23, which is lower than Ampicillin-Gentamicin therapy whch is of IDR 9,730,746.21, thus showing that Seftriaxone-Gentamicin is more *cost-effective* than Ampicillin-Gentamicin. The ICER calculation has negative result of Idr 500,953.74 so it shows that the Ceftriaxone-Gentamicin combination antibiotic is more *cost-effective*.

Keywords **:** Ampicillin – Gentamicin, Cost Effectiveness, Ceftriaxone-Gentamicin

INTRODUCTION

Excellent health service is a demand of the community (Aisyah, 2015). In an effort to optimize health services, the government has created a national health insurance program that can help people to get the best health services (Nadiyah et al., 2017).

In Indonesia in recent years, data on the cost of health services has shown to be increasing, this is caused by various reasons, including changes in disease and treatment patterns, an increase of using of advanced technology in handling disease cases, an increasing of public demand, and because of the global economy changes and on the other hand the costs provided by the government for health services has not been improved, where the government's ability is increasingly limited and the role of the community is still not optimal (Admaja et al., 2019)

Medicine is an important component in a health service. One of the drugs with a high amount of demand is antibiotics (Williams, 2016). However, the high demand for antibiotics

in infectious cases turned out to cause a big problem for BPJS (Social Security Agency on Health). Pneumonia cases caused by this infection are the second cause of death in children aged less than 5 years (Nadiyah et al., 2017).

In Madiun, 620 pneumonia cases were found in toddlers which were spread across several publich health centers (puskesmas) and hospitals based on Madiun city health profile data in 2019. Pneumonia is characterized by fever, chills, coughing up phlegm, and breathing difficulty. The bacteria that commonly causes pneumonia is Streptococcus pneumoniae.

In developing countries, including Indonesia, hospitalized patients who receive antibiotic therapy reach 30-80%. However, of these percentages, as many as 20-65% indicates improper use of it which resulting in resistance and more costs (Fair & Tor, 2014).

The antibiotic used at Hospital X in Madiun is a combination therapy of Ceftriaxone-Gentamicin and Ampicillin-Gentamicin where there are differences in the structure and pharmacokinetics of Ceftriaxone and Ampicillin that can affect their effectiveness, therefore, considerations are needed on the efficiency of therapeutic use in medicine and pharmacoeconomic studies have an important role as a description and analysis of therapeutic costs in a health care system. Pharmacoeconomics is a comprehensive study to determine the economic effect of alternative drug therapies or other interventions. One of the analytical methods in pharmacoeconomics is Cost Effectiveness Analysis (CEA). CEA results are described in ratios divided into ACER (Average Effectiveness Ratio) and ICER (Incremental Cost Effectiveness Ratio)

METHODS

The study was conducted in an analytical observational manner using a *cross-sectional* research design conducted retrospectively with the aim of determining the cost-effectiveness of the use of ceftriaxone-gentamicin and ampicillin-gentamicin combination antibiotics in cases of pneumonia on paediatrics at hospital X in Madiun. The cost is calculated from the perspective of the provider in this case is the hospital spent towards direct medical costs during the patient's inpatient treatment at the hospital. The samples in this study were patients with a diagnosis of pneumonia aged ≤ 12 years who were undergoing hospitalization. Patients without complications condition received a combination of ceftriaxone-gentamicin and ampicillin-gentamicin antibiotic therapy, with purposive sampling techniques using collection sheets. The analysis technique uses was decision analysis (Decision Tree).

RESULTS

Based on inclusion and exclusion criteria, 39 patient samples were obtained, a total of 16 patients received Seftriaxone-Gentamicin antibiotic therapy, the number of patients were lower than patients with Ampicillin-Gentamicin therapy which was 23 patients (Table 1).

Table 1. Patient characteristics

Characteristic		Therapy Group		Percentage (%)
		Ceftriaxone-Gentamicin	Ampicillin-Gentamicin	
Number of Patients		16	23	100%
Gender	Males	11	10	54%
	Females	5	13	46%
Aged	0 – 3 month	7	10	44%
	4 – 12 month	3	5	21%
	1 – 5 year	6	7	33%
	6 – 12 year	0	1	2%
Therapeutic Outcomes based on LOS	≤ 6 days	13	18	79%
	> 6 days	3	5	21%

Referring from the frequency of gender, the number of male patient samples were 21 samples (54%) more than female which were 18 samples (46%), while based on age, patients with Ceftriaxone-Gentamicin antibiotic therapy there were 7 patients (44%) aged 0-3 months, there were 3 patients (19%) aged 4-12 months, there were 6 patients (37%) aged 1-5 years, and there was no patients aged 6-12 years. Meanwhile, the number of patients with antibiotic therapy Ampicillin-Gentamicin, there were 10 patients (44%) aged 0-3 months, there were 5 patients (22%) aged 4-12 months, there were 7 patients (30%) aged 1-5 years, and there was 1 person (4%) patients aged 6-12 years.

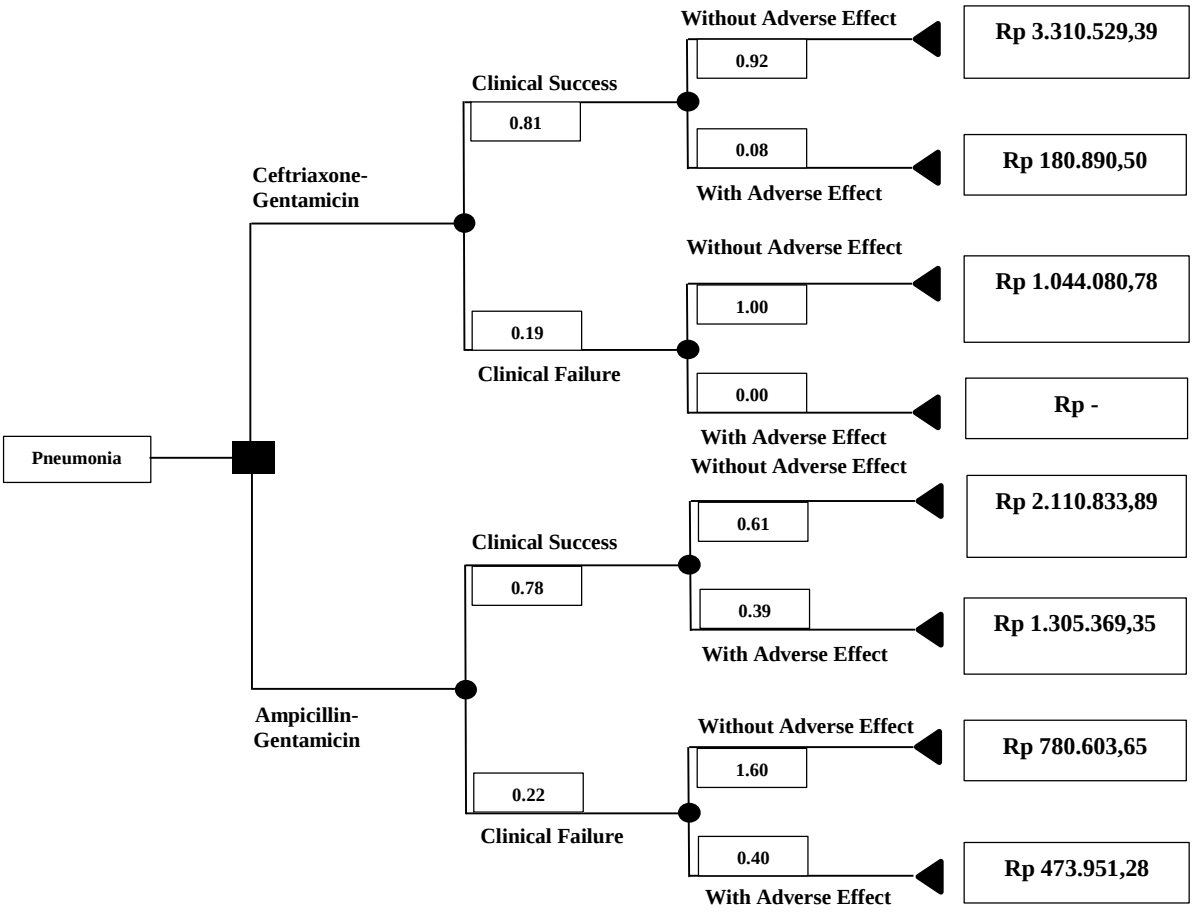
Based on the outcome, patients who met the target of ≤ 6-day therapy were 31 patients (79%) out of a total sample of 39 (100%). A total of 13 patients (81%) out of 16 patients with the Seftriaxone-Gentamicin combination met the therapeutic target more than patients with Ampicillin-Gentamicin, which had 18 patients.

Table 2. Direct Medical Costs of Patients with Ceftriaxone-Gentamicin Therapy

Types of costs	**Average costs (Rp)**	**Total costs (Rp)**
Cost of Antibiotics	128.512	2.056.189
Cost of Supporting Medicine	436.776	6.988.410
Cost of Medicines for Adverse effects	15.860	15.860
Cost of Hospital Care	3.850.946	61.615.141
Cost of Medical Support	119.441	1.911.060
Total Direct Medical Cost		72.586.660
Average of Total Direct Medical Costs		4.536.666

Table 3. Direct Medical Costs of Patients with Ampicillin-Gentamicin Therapy

Types of costs	**Average costs (Rp)**	**Total costs (Rp)**
Cost of Antibiotics	147.808	3.399.582
Cost of Supporting Medicine	383.367	8.817.435
Cost of Medicines for Adverse effects	20.429	183.860
Cost of Hospital Care	3.992.359	91.824.265
Cost of Medical Support	135.913	3.126.008
Total Direct Medical Cost		107.351.150
Average of Total Direct Medical Costs		4.667.441



The results showed that the total direct medical cost of Seftriaxone-Gentamicin combination therapy amounted to Rp 72,586,660 with an average cost spent by patients was Rp 4,536,666 (Table 2). While the total direct medical cost of the Ampicillin-Gentamicin combination was Rp 107,351,150 with the average cost spent by patients was up to Rp 4,667,441 (Table 3).

Picture 1. Decision tree Ceftriaxone-gentamicin and Ampicillin-gentamicin

Table 4. The Probability value of Therapyy Outcome

Antibiotics	Outcome Parameter	Total	Probability Value	Percentage (%)
Ceftriaxone-Gentamicin	Success (≤ 6 days)	13	0,81	81
	Failed (> 6 days)	3	0,19	19
	Success Without Adverse effects	12	0,92	92
	Success With Adverse effects	1	0,08	8
	Failed Without Adverse effects	3	1	100
	Failed With Adverse effects	0	0	0
Ampicillin-Gentamicin	Success (< 7 days)	18	0,78	78
	Failed (> 6 days)	5	0,22	22
	Success Without Adverse effects	11	0,61	61
	Success With Adverse effects	7	0,39	39
	Failed Without Adverse effects	3	0,60	60
	Failed With Adverse effects	2	0,40	40

It can be seen from table IV, that the probability value of successful Seftriaxone-Gentamicin therapy without adverse effects was 0.92, which was higher than Ampicillin-Gentamicin therapy of 0.61. Meanwhile, the probability value of successful Seftriaxone-

Gentamicin therapy with adverse effects was 0.08 which was lower than patients who received Ampicillin-Gentamicin, which was 0.39. There were also failed therapies (> 6 days) from each therapy group. Total patients with unsuccessful ceftriaxone-Gentamicin therapy without adverse effects (1.00). Meanwhile, the probability value of Ampicillin-Gentamicin therapy that failed without adverse effects was 0.60 and that therapy which failed with adverse effects was 0.40.

Table 5. Calculation of Direct Medical Cost per Outcome of the Theraphy

Antibiotics	**Types of Costs**	***Outcome***				**Total EMV**
		Success without Adverse effects	**Success with Adverse effects**	**Failed without Adverse effects**	**Failed with Adverse effects**	
Ceftriaxone-Gentamicin	Cost of Antibiotics	128.677,00	81.639,00	143.476,00	-	4.535.500,67
	Cost of Supporting Medicine	435.628,00	170.216,00	530.218,00	-	
	Cost of Medicines for Adverse effects	-	15.860,00	-	-	
	Cost of Hospital Care	3.750.494,00	2.467.305,00	4.713.968,00	-	
	Cost of Medical Support	127.672,00	56.500,00	107.500,00	-	
Total Average Cost		4.442.471,00	2.791.520,00	5.495.162,00	0,00	
Total of *x* Outcome		3.310.529,39	180.890,50	1.044.080,78	0,00	
Ampicillin-Gentamicin	Cost of Antibiotics	122.468,00	133.643,00	223.285,00	223.440,00	4.670.758,17
	Cost of Supporting Medicine	381.773,00	343.439,00	446.886,00	436.599,00	
	Cost of Medicines for Adverse effects	-	19.591,00	-	23.363,00	
	Cost of Hospital Care	3.796.975,00	3.643.677,00	5.118.827,00	4.597.658,00	
	Cost of Medical Support	135.173,00	150.805,00	124.667,00	104.750,00	
Total Average Cost		4.436.389,00	4.291.155,00	5.913.665,00	5.385.810,00	
Total of *x* Outcome		2.110.833,89	1.305.369,35	780.603,65	473.951,28	

In the success therapy without adverse effects, the average cost of Seftriaxone-Gentamicin therapy was Rp. 4,442,471.00, which was higher than Ampicillin-Gentamicin therapy, which was Rp.4,436,389.00. In the success therapy with adverse effects, the average cost of Seftriaxone-Gentamicin therapy was Rp 2,791,520.00 which was lower than Ampicillin-Gentamicin therapy which was Rp 4,291,155.00 (Table 5). The probability and average cost per outcome of therapy are expressed in the decision tree (Figure 1). From the calculation results, it was found that the total EMV for Seftriaxone-Gentamicin therapy was Rp. 4,535,500.67 which was lower than Ampicillin-Gentamicin which was Rp. 4,670,758.17. The

EMV value generated through decision tree analysis will then be calculated by the ACER and ICER calculation values.

Table 6. ACER and ICER calculations

Antibiotics	Cost (Rp)	Effectiveness	ACER (Rp)	ICER (Rp)
Ceftriaxone-Gentamicin	4.535.500,67	0,75	6.047.334,23	- 500.953,74
Ampicillin-Gentamicin	4.670.758,17	0,48	9.730.746,21	
Incrementals	- 135.357,51	0,27	- 3 683.411,98	

From the decision tree analysis, the total cost of Expected Monetary Value (EMV) of Ceftriaxone-Gentamicin and Ampicillin-Gentamicin therapy is generated. The EMV value for Seftriaxone-Gentamicin therapy was Rp. 4,535,500.67 lower than Ampicillin-Gentamicin which was 4,670,758.18.

DISCUSSION

Based on the medical record data obtained at Hospital X Madiun for the 2022 period, there were 80 patients for pediatric pneumonia cases. Of the total patients, only a few could meet the inclusion and exclusion criteria to be the samples in this study, namely pediatric pneumonia patients with ceftriaxone-gentamicin combination antibiotic therapy, which of 16 patients, while patients with ampicillin-gentamicin therapy were 23 patients

According to the Ministry of Health in 2004, gender is one of the risk factors for pneumonia. Male toddlers have differences in hormonal systems with female toddlers. The hormonal system can affect the resistance in the body of male toddlers to be more susceptible to bacterial and viral infections that can cause pneumonia. The high risk of pneumonia in male todlers is also supported due to physical differences in respiratory anatomy. The respiratory tract in male todlers tends to be smaller than female todlers (Sumiyati, 2015). When it is viewed from socio-cultural point of view, male todlers play more outdoors so they tend to be exposed to air pollution outside the home. Pollution outside the home includes dust, cigarette smoke, motor vehicle smoke, so that male toddlers are susceptible to respiratory diseases such as pneumonia (Setyoningrum &; Mustiko, 2020).

The difference in the length of treatment days in patients could be correlated to the effectiveness of antibiotic therapy. Ceftriaxone has high antibacterial potential, a broad spectrum against gram-negative and gram-positive bacteria and has low toxicity (Nalang et al., 2018). The difference in effectiveness is also influenced because ampicillin has a plasma half-life ranging from 1 – 1.5 hours, while in ceftriaxone is 6 – 9 hours. The half-life is related to the elimination of the drug. The longer the half-life of the drug, the longer the body can eliminate the drug entirely (Noviani and Nurilawati, 2017), besides that the difference in the length of treatment can also be caused by the emerging of the adverse effects from the drug usage. Based from the incidence of emerging of the adverse effects, the most incidence of Ampicillin-Gentamicin usage is causing diarrhea. As many as 7 (39%) out of 18 patients who achieved the target therapy ≤ 6 days on the use of Ampicillin-Gentamicin experienced diarrhea lower than Seftriaxone-Gentamicin therapy which was only found in 1 patient (8%). In the failed Seftriaxone-Gentamicin therapy there was no adverse effects found, while in the failed Ampicillin-Gentamicin therapy there was found 2 patients (9%) had diarrhea. Diarrhea in pediatric pneumonia patients at RSUD (Regional Public Hospital) Madiun can be caused by adverse effects of using Ampicillin. Ampicillin is known to cause disruption of the composition and function of the normal intestinal flora (Barbut, 2002).

The length of the day of treatment affects the amount of direct medical costs needed by the patients. The longer the patient's LOS (the average days of hospital care), the higher the need for antibiotics, supporting drugs, and medical actions taken. The EMV result is then calculated in the form of a ratio through the ACER calculation. Based on ACER calculations,

the ACER value in Seftriaxone-Gentamicin antibiotic therapy was Rp. 6,047,334.23 which was lower than Ampicillin-Gentamicin therapy which was Rp. 9,730,746.21 so it shows that Seftriaxone-Gentamicin is more cost effective than Ampicillin-Gentamicin. The calculation of the ICER value showed a negative result of Rp 500,953.74 so that it can be interpreted that the Seftriaxone-Gentamicin combination therapy required smaller cost and is more effective in the treatment of pneumonia in pediatrics than the Ampicillin-Gentamicin combination.

CONCLUSION

Based on the results and discussion, it can be concluded that the value of ACER Seftriaxone-Gentamicin with a value of Rp 6,047,334.23 is more cost effective than the combination of Ampicillin-Gentamicin with a value of Rp 9,730,746.21. An ICER value of – Rp 500,953.74 indicates that the Seftriaxone-Gentamicin combination requires a lower cost with higher effectiveness

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